Message

From: Kumar, Manisha [Kumar.Manisha@epa.gov]
on behalf of Science and Technology Policy Council Staff [STPC_Staff@epa.gov]
Sent: 8/28/2017 5:43:20 PM
To: Armstead, John A. [Armstead.John@epa.gov]; Barone, Stan [Barone.Stan@epa.gov]; Canzler, Erica [Canzler.Erica@epa.gov]; Etzel, Ruth [Etzel.Ruth@epa.gov]; Fine, Steven [fine.steven@epa.gov]; Greene, Mary [greene.mary@epa.gov]; Heard, Anne [Heard.Anne@epa.gov]; Kavlock, Robert [Kavlock.Robert@epa.gov]; McGartland, Al [McGartland.Al@epa.gov]; Minoli, Kevin [Minoli.Kevin@epa.gov]; Newton, Cheryl [Newton.Cheryl@epa.gov]; Rodan, Bruce [rodan.bruce@epa.gov]; Rodrigues, Cecil [rodrigues.cecil@epa.gov]; Shapiro, Mike [Shapiro.Mike@epa.gov]; Shaw, Betsy [Shaw.Betsy@epa.gov]; Simon, Harvey [Simon.Harvey@epa.gov]; Simon, Nigel [Simon.Nigel@epa.gov]; Sinks, Tom [Sinks.Tom@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Zarba, Christopher [Zarba.Christopher@epa.gov]
CC: STPC_SSP [STPC_SSP@epa.gov]; Science and Technology Policy Council Staff [STPC_Staff@epa.gov]
Subject: STPC Concurrence Requested on the RAF Report: State of the Science Review: Variability Estimates in Human Health Dose-Response Characterization
Attachments: SoS Review Human Variability 5-24-2017.docx

Good afternoon,

STPC members are requested to provide their concurrence on the Risk Assessment Forum (RAF) Report: *State of the Science Review: Variability Estimates in Human Health Dose-Response Characterization* (attached below), using the following link, by **Friday, September 15, 2017**.

SoS Review Human Variabilit...

Concurrence form link: https://goo.gl/forms/m2Gf1RcBtcYHGM862

Please contact Tom Sinks (Sinks.Tom@epa.gov) or Ed Ohanian (Ohanian.Edward@epa.gov) if you have any questions about this Report. If you have any issues with the concurrence form, please try placing the URL in a different browser (e.g., Google Chrome) or contact Anand Mudambi at 202-564-2817.

Background on the Report:

This report was developed by the Risk Assessment Forum in response to two important recommendations made by the 2009 National Research Council (NRC) report *Science and Decisions* to EPA:

1. A recommendation to revisit default values used in risk assessments, including those used in deriving Reference Dose (RfD)/Reference Concentration (RfC). The uncertainty factor for human variability is a primary example of the defaults referred to in this recommendation.

2. A recommendation to adopt a new framework for dose-response assessment, and corresponding implementation recommendations that would replace single point value uncertainty factors with distributions including the need for unification of cancer and noncancer approaches in which chemicals are put into a common analytic framework regardless of type of outcome.

RfD and RfC are important inputs commonly used in EPA risk assessments. One of the uncertainty factors used in RfD/RfC derivation represents human variability (also referred to as the intraspecies uncertainty factor) - a default factor of 10 is used to represent the magnitude of potential difference in susceptibility to a given

chemical between a median human and more sensitive humans. The ten-fold human variability factor is generally assumed to consist of two components – a factor of 3 for human toxicokinetic variability, and a factor of 3 for human toxicodynamic variability.

This report considered several types of data that may be useful for estimation of human variability, including both traditional data sources and newer science including:

- controlled human exposure studies;
- human epidemiological studies;
- animal models;
- in vitro studies of toxicodynamic variability; and
- in vitro and in silico models of toxicokinetic variability.

Each type of data considered has advantages and limitations in potential application to quantifying human variability. In addition, each has varying potential for providing substantial new data for quantifying human variability over the next several years. In vitro studies appear to provide the greatest opportunity for substantial near-term advances.

This report recommends that EPA should reach out to scientists conducting research that generate these types of data to make them aware of the potential applications of their study techniques to estimate human variability for use in environmental risk assessment. This outreach and collaboration would likely result in enhancements to their study designs, statistical techniques, and results reporting to further quantify variability across the population in response to chemical exposures.